Psychiatric Drugs

Training Lecture #1
Grace E. Jackson, MD

(last revised: 10/21/10)

Introduction

My name is Dr. Grace Jackson. This presentation was originally prepared by me in 2010, when I was working as a clinician and Medical Director within several agencies that deliver publicly funded services to the mentally ill. The information which appears below is intended for health care professionals and non-professionals alike, in order to introduce the important association between psychiatric drugs, medical illness, and premature death.

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This presentation was entirely self-funded by the author with no outside support. Between 2003 and 2008, the author served as an expert witness in several civil cases involving privacy and patient autonomy (the right to decline toxic drugs). In 2007 and 2008, the author provided written testimony on behalf of plaintiffs in three product liability cases involving antidepressants and suicide. The author owns no stock holdings or patents in pharmaceutical companies or their products. The author has never participated in pharmaceutical company speakers' bureaus or advisory boards, has never received pharmaceutical company funding for research or travel, and has never participated in the ghostwriting or sponsored authorship of publications. The author is not employed, paid, or sponsored by any religious organization or church, academic department, medical school, contract research organization, or association of mental health or medical professionals.

Outline of Lecture

I. Major Classes of Psychiatric Drugs
II. America's Drug Problem
III. Killing the Mentally Ill
IV. Psychiatric Drug Toxicity

This presentation has four goals:

1) to introduce the major families of psychiatric medications

2) to explain current trends in the USA's consumption of pharmaceuticals

3) to describe the kinds of medical conditions which commonly affect patients who receive mental health care from publicly funded sources (e.g., Medicaid)

and

4) to explain the serious health risks which are associated with psychiatric drug treatments.

I. Types of Psychiatric Drugs

6 Major Classes of Psych Drugs

- Antidepressants
- Antipsychotics
- Mood Stabilizers
- Sedative Hypnotics / Anxiolytics
- Stimulants
- “Anti”-Addiction Drugs

Although chemicals have long been used throughout history to alter cognition, mood, and behavior, the so-called “psychopharmaceutical era” originated in the late 19th and mid-20 centuries.

The Food and Drug Administration is the U.S. governmental agency which approves and regulates medications. Currently, there are more than 100 different pharmaceuticals which have received FDA “approval” for the treatment of psychiatric conditions.

Excluding the chemicals which are specifically used to treat nicotine (varenicline), alcohol (disulfiram, acamprosate) and opioid dependence (naltrexone, methadone, buprenorphine), there are six major categories of psychotropic drugs:

antidepressants	
antipsychotics	(sometimes called “major” tranquilizers)
mood stabilizers	(anticonvulsants and lithium)
sedatives/anxiolytics	(sometimes called “minor” tranquilizers)
stimulants	
“anti-addiction” drugs	

II. America's Drug Problem

Question #1

Question #1

Most Common Disease (point prevalence)

a) asthma
b) Alzheimer's
c) diabetes
d) arthritis

In any given year, which of the aforementioned medical conditions afflicts the greatest number of people within the U.S.A.?

Question #1
Most Common Disease

d) arthritis ☑

This answer may be surprising to many readers. However, according to the Centers for Disease Control (CDC), **arthritic conditions** affect approximately 46 million (1 in 5) residents within the U.S.A. [Source: CDC 2009]

This statistic, drawn from the "National Health Interview Survey," reflects the following prevalence rates for a variety of rheumatological / skeletal conditions [Source: Arthritis and Rheumatism, 2008]

	Osteoarthritis	27 million
	Fibromyalgia	5 million
	Gout	3 to 6 million
	Rheumatoid arthritis	3 million
	Primary sjogren's syndrome	1.3 million
	Polymyalgia rheumatica	711,000
	Spondyloarthritdes ankylosing spondylitis, reactive arthritis, psoriatic arthritis enteropathic arthritis	639,000 to 2.4 million
	Juvenile RA	294,000
	Giant Cell Arteritis	228,000
	Systemtic lupus	161,000 to 322,000
	Systemic sclerosis (scleroderma)	49,000
Oddballs:	carpal tunnel	1 to 10 million
	low back pain within past 3 months	59 million
	neck pain in past 3 months	30 million

Somatic vs. Psychiatric

Lifetime Prevalence - USA

cancer	30-50%	depression	16%
arthritis	~ 20%	specific phobia	9%
asthma	12%	ADHD	5%
diabetes	9%	PTSD	3.5%
MI/angina	7%	bipolar	3%
stroke	3%	panic	3%
epilepsy	3%	OCD	1%
dementia	2%	schizophrenia	1%

This slide compares the lifetime prevalence rates for various diseases of the human body (somatic conditions) versus the prevalence rates for various phenomena which affect the mind or soul (psychiatric conditions).

The key point to be made is that chronically or recurrently psychotic states – such as those which result in the diagnosis of “schizophrenia” or “bipolar disorder” – affect a strikingly small percent of the population.

Question #2

Question #2
Top Selling Drug Class in the U.S.A.

a) cancer medicines
b) insulin
c) asthma inhalers
d) antipsychotics

Question #2
Top Selling Drug Class in the U.S.A.

d) antipsychotics ☑

U.S. Drug Sales 2009

[IMS Health]

Total Drug Sales		300.3 billion
APs	#1	14.6 billion
lipid	#2	14.3 billion
PPI	#3	13.6 billion
ADs	#4	9.9 billion
insulin	#9	6.3 billion
stimulants	#11	5.8 billion
seizure	#13	5.3 billion

APs = antipsychotics
ADs = antidepressants

According to *IMS Health, U.S. sales of antipsychotics (AP) totaled 14.6 billion dollars in 2009. Antidepressant (AD) sales in the United States amounted to 9.9 billion dollars. Sales of stimulants (e.g., drugs used to treat the symptoms of childhood hyperactivity and inattention) and anti-seizure drugs accounted for 5.8 billion dollars and 5.3 billion dollars, respectively.

*IMS Health is a “market intelligence” company. By using a computerized network which collects data from global healthcare markets, IMS tracks over 70% of the world’s

pharmaceutical sales transactions and over 90% of the U.S. pharmaceutical sales transactions each day.

of U.S. Prescriptions - 2009

[IMS Health]

Total Prescriptions		3.9 billion
lipid	#1	210.5 million
codeine	#2	200.2 million
ADs	#3	168.7 million
ACEi	#4	162.8 million
AEDs	#7	104.5 million
benzos	#11	87.9 million
arthritis	#13	77.9 million

Key:

AD	= antidepressants
ACEi	= ACE inhibitors (a class of drugs which lower blood pressure)
AED	= antiepileptic drugs (anticonvulsants)
benzos	= benzodiazepines (e.g., diazepam, clonazepam, alprazolam)

In terms of U.S. **prescription volumes** in 2009, lipid lowering drugs (e.g., statins) and codeine or codeine combinations (synthetic painkillers) were the dominant drugs.

Interestingly, three families of neuropsychiatric medications were commonly prescribed. Antidepressants were the third most dominant drug class in terms of # of prescriptions dispensed (168.7 million prescriptions). AED (anti-epileptic drugs, which are used not only for seizure disorders, but increasingly for control of mood swings, aggression, and misbehavior) placed seventh (104.5 million prescriptions). Benzodiazepines (so-called “minor tranquilizers” or anti-anxiety drugs) finished eleventh.

U.S. = 4.5 % of world population

90% of stimulant sales
63% of AP sales
51% of AD sales
41% of AED sales

Although the U.S. population comprises only 4.5% of the planet's human inhabitants, Americans account for a disproportionate share of the world's pharmaceutical sales:

90% of the world's stimulants
63% of the world's antipsychotics
51% of the world's antidepressants
41% of the world's anti-epileptics

[Source of sales data: IMS Health]

U.S.A.: Psychiatric Drugs 2009

[Source: Express Scripts 2009 Drug Trend Report]

antidepressants	9.9%	31,000,000
anticonvulsants	4.0%	12,300,000
stimulants	2.2%	6,754,000
*antipsychotics	1.8%	5,526,000

*part of Express Scripts' "mental/neurological" class:
includes lithium, dementia drugs, sub. abuse

Express Scripts, a pharmaceutical benefits management company, produces annual drug trend reports. The information in this slide was obtained from the most recent Drug Trend Report (published in April 2010). Approximately 10% of U.S. residents used an antidepressant at some time in 2009; 4% used anticonvulsants; 2% used stimulants; and approximately 2% used an antipsychotic.

These numbers exclude drug use by non-commercially insured patients, such as veterans and active duty military personnel; institutionalized patients (e.g., residents of nursing homes, prisons, jails, and state hospitals); and patients who rely upon publicly funded programs, such as Medicaid and Medicare.

How Did They Do It:

Prescription drug use was evaluated by examining pharmacy claims from two independent, random samples of approximately 3 million commercially insured individuals. The prevalence of use was calculated by dividing the # of insured members taking medications in a certain drug class by the total number of insured.

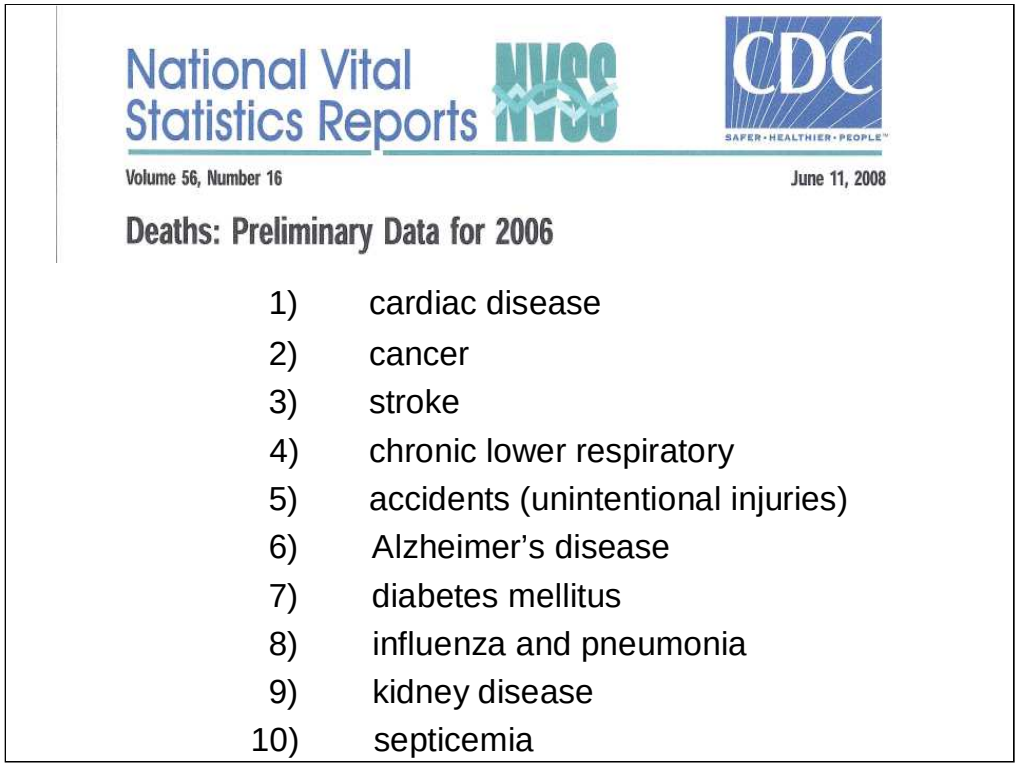
To place the aforementioned figures in context, the Express Scripts database revealed the following patterns of non-psychiatric drug use in 2009:

pain killers	17.8%
heart disease, hypertension	15.7%
high cholesterol drugs	12.1%
asthma medications	8.7%
ulcer disease (antacids)	8.2%
diabetes	5.0%
anti-virals	4.5%

Question #3

Question #3
Leading Cause of Death in the U.S.A.

a) heart disease
b) HIV/AIDS
c) stroke
d) cancer



The federal government collects and analyzes vital statistics and publishes the results in annual summaries. Each year, approximately 0.8% of the entire U.S. population succumbs to illnesses or accidents (roughly 2.4 million deaths per year).

According to the Centers for Disease Control (National Vital Statistics Report – preliminary data), the leading causes of death in the United States in 2006 were:

cause of death	# of deaths
major cardiac disease	629,191
cancer	560,102
stroke	137,265
chronic lower respiratory diseases	124,614
accidents (excluding suicides)	121,599
Alzheimer's disease	73,177
diabetes	72,507
influenza and pneumonia	56,247
septicemia	44,791

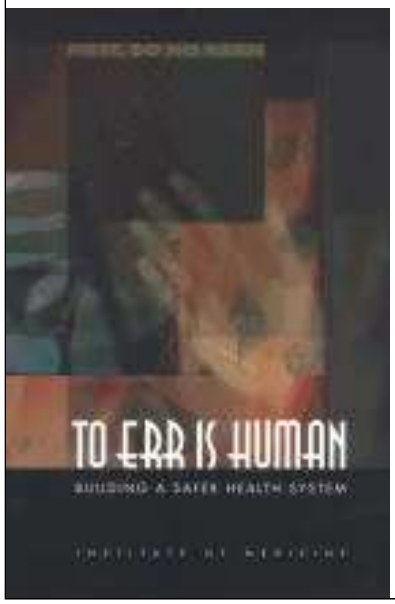
Question #3
Leading Cause of Death in the U.S.A.

a) heart disease ☑

but . . . this is only part of the story…

Institute of Medicine (1999)

44,000 to 98,000 dead from errors



Types of Errors

Diagnostic
- Error or delay in diagnosis
- Failure to employ indicated tests
- Use of outmoded tests or therapy
- Failure to act on results of monitoring or testing

Treatment
- Error in the performance of an operation, procedure, or test
- Error in administering the treatment
- Error in the dose or method of using a drug
- Avoidable delay in treatment or in responding to an abnormal test
- Inappropriate (not indicated) care

Preventive
- Failure to provide prophylactic treatment
- Inadequate monitoring or follow-up of treatment

Other
- Failure of communication
- Equipment failure
- Other system failure

SOURCE: Leape, Lucian; Lawthers, Ann G.; Brennan, Troyen A., et al. Preventing Medical Injury. Qual Rev Bull. 19(5):144–149, 1993.

In 1999, the Institute of Medicine stunned many medical professionals and policy makers with an analysis of America's healthcare system. In its report entitled *To Err Is Human*, the Institute of Medicine estimated that at least 44,000 and as many as 98,000 people die in America's hospitals each year as a result of preventable errors.

Included in this analysis of hospital-related errors were wrong or delayed diagnoses, errors in drug doses or method of drug delivery, inadequate monitoring, and avoidable delays in responding to abnormal tests.

JAMA (2000)

COMMENTARY

Is US Health Really the Best in the World?

☠ ADVERSE EFFECTS ☠

106,000 inpatient deaths
199,000 outpatient deaths

305,000 deaths from Rx

The following year, the prestigious *Journal of the American Medical Association* (aka, JAMA) featured an article by Johns Hopkins University professor, Dr. Barbara Starfield. The article expanded upon the Institute of Medicine's theme of iatrogenic (treatment-related) death.

Using data culled from a variety of inpatient and outpatient investigations, Starfield's analysis estimated that adverse effects of medication (i.e., "therapeutic" doses of prescription drugs taken exactly as prescribed) account for approximately 305,000 deaths per year.

106,000 inpatient deaths due to pharmaceuticals
199,000 outpatient deaths due to pharmaceuticals

[Note: Given the fact that "adverse drug reactions" are rarely reported, and given the fact that drug-related heart attacks, strokes, pneumonias, and cancers are seldom attributed by physicians or governmental agencies to pharmaceuticals, these estimates were absurdly conservative.]

Reality Check: # of deaths (2006)

1.	cardiac disease	629,191
2.	cancer	560.102
3.	adverse drug reactions	305,000
4.	stroke	137,265
5.	accidents	124,614
6.	medical errors	98,000
7.	Alzheimer's disease	73,177
8.	diabetes mellitus	72,507
9.	flu & pneumonia	56,247
10.	septicemia	44,791

If one integrates the aforementioned statistics within the previous governmental listing of America's top causes of death, the results are striking:

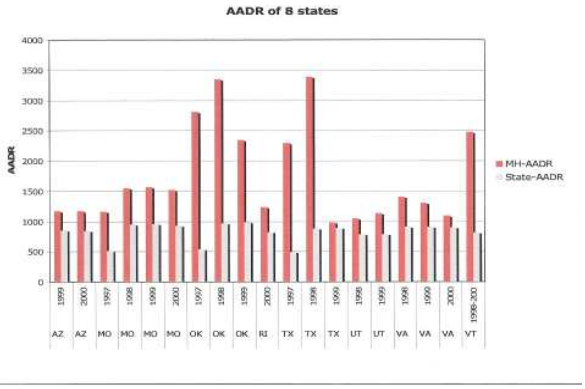
- **adverse drug reactions become the third leading killer in the U.S.A.**
- **medical errors become the sixth leading killer in the U.S.A.**

III. What's Killing the Mentally Ill

Morbidity and Mortality in Public MH Patients

[Sources: 2006 - Colton & Manderscheid & NASMHPD 13th Technical Report]

16 State Study Results: Age Adjusted Death Rate



annual death rates

SMI 1 - 3.5%

non-SMI 0.5 - 0.8%

In 2006, two pivotal papers summarized the results of a federally funded study of mortality (death rates) among public mental health patients. Sponsored by the Center for Mental Health Services and the National Association of State Mental Health Program Directors, the investigation solicited data from sixteen states. Eight states returned information on the death rates for patients with Serious Mental Illness (SMI).

This slide depicts annual age-adjusted death rates for SMI vs. the non-mentally ill.

Specifics of the study:

1) data were collected for public mental health patients receiving services between 1997 and 2000

2) SMI (serious mental illness) included major depression, bipolar disorder, schizophrenia, and ADHD

3) in all 8 states which participated (AZ, MO, OK, RI, TX, UT, VA, and VT), the seriously mentally ill had higher rates of death than the general population

4) when matched by age to non-mentally ill individuals, patients with SMI died at an earlier age --
on average, the SMI patients died 13 to 30 years earlier than expected
mean age at time of death: 49-60

5) most mental health patients died of natural causes, such as heart disease and respiratory conditions

Key limitations of the study:

>> investigators did not consider the prevalence of dementia or dementia-related deaths

>> investigators did not consider the role of medication in the deaths of those diagnosed with SMI

Table 2. Mean Age at Time of Death for Public Mental Health Clients and Mean Number of Years of Potential Life Lost (YPLL) per Public Mental Health Client Who Died During a Year in Which a Service Was Received[a]

State and Year	Mean Age at Time of Death, y			Mean Number YPLL Per Deceased Mental Health Client[b]
	All Clients Who Died During Year	Male Clients Who Died During Year	Female Clients Who Died During Year	
Arizona				
1999	48.9	47.5	52.3	32.2
2000	49.6	48.5	52.7	31.8
Missouri				
1997	58.3	54.4	61.8	26.3
1998	56.9	53.6	60.6	27.3
1999	58.0	54.1	61.3	26.8
2000	56.4	53.1	59.4	27.9
Oklahoma				
1997	59.9	54.6	65.0	25.1
1998	59.9	53.2	65.3	25.1
1999	58.9	52.0	64.6	26.3
Rhode Island				
2000	60.2	53.4	65.5	24.9
Texas				
1997	55.0	52.4	58.1	28.5
1998	55.0	53.3	56.6	28.8
1999	54.0	50.8	57.3	29.3
Utah				
1998	55.1	47.2	63.8	29.3
1999	58.4	53.7	63.2	26.9
Virginia[c]				
1998	72.4	70.6	74.8	15.5
1999	74.4	72.5	76.9	14.0

13 to 30 yrs of life lost

This slide (drawn from the aforementioned study) depicts the average age of death among public mental healthcare recipients diagnosed with Serious Mental Illness.

The column on the far right depicts the mean number of "Years of Potential Life Lost" per mental health patient.

Key Points:

On average, recipients of public mental healthcare in the U.S.A. were dying in the late 1990s approximately 13 to 30 years earlier than expected.

Although these data are now dated (1997 to 2000), they quite likely underestimate the scope of existing mortality among Americans with SMI. The reasons for this continuing crisis include factors which will be discussed below.

Causes of death 1997 2000…

SMI	% of deaths	non-SMI	% of deaths
cardiac	17-31%	cardiac	21-30%
cancer	5-10%	cancer	18-22%
suicide	5-9%	stroke	5%
chronic respiratory	4-5%	chronic respiratory	2-4%
stroke	2-5%	diabetes	2%
diabetes	1-3%	suicide	0.3-1%

Missing from the discussion: dementia

Data collected from all eight states revealed that patients with SMI died primarily of the same "natural" causes which affected the non-mentally ill: cardiac disease, cancer, stroke (cerebrovascular disease), chronic respiratory conditions, and diabetes.

However, a major limitation of the published technical report and supporting paper (Colton and Manderscheid) was the failure of the researchers to address iatrogenic (treatment-related) causes of premature death.

Among the most significant limitations of the published report were the authors' and editors' --

- failure to discuss the role of dementia in death rates of those with SMI
- failure to discuss the role of pharmaceuticals as a cause of dementia
- failure to discuss the role of pharmaceuticals as a cause of suicide

Interestingly, cancer-related deaths were less common among people with SMI. One of the reasons for this finding may relate to the heavy use of pharmaceuticals by recipients of publicly funded healthcare. With few exceptions, the various families of psychiatric drugs have been found to possess cancer-fighting properties. Unfortunately, these same biological effects more than likely contribute to the teratogenicity (miscarriages and birth-defects) and multiple systemic toxicities of the same chemicals.

Time trends in schizophrenia mortality in Stockholm County, Sweden: cohort study

BMJ 2000

Urban Ösby, Nestor Correia, Lena Brandt, Anders Ekbom, Pär Sparén

Observed over expected numbers of deaths and relative risks (95% confidence intervals) for different causes of death in patients first admitted to hospital with schizophrenia, Stockholm County, 1976-95

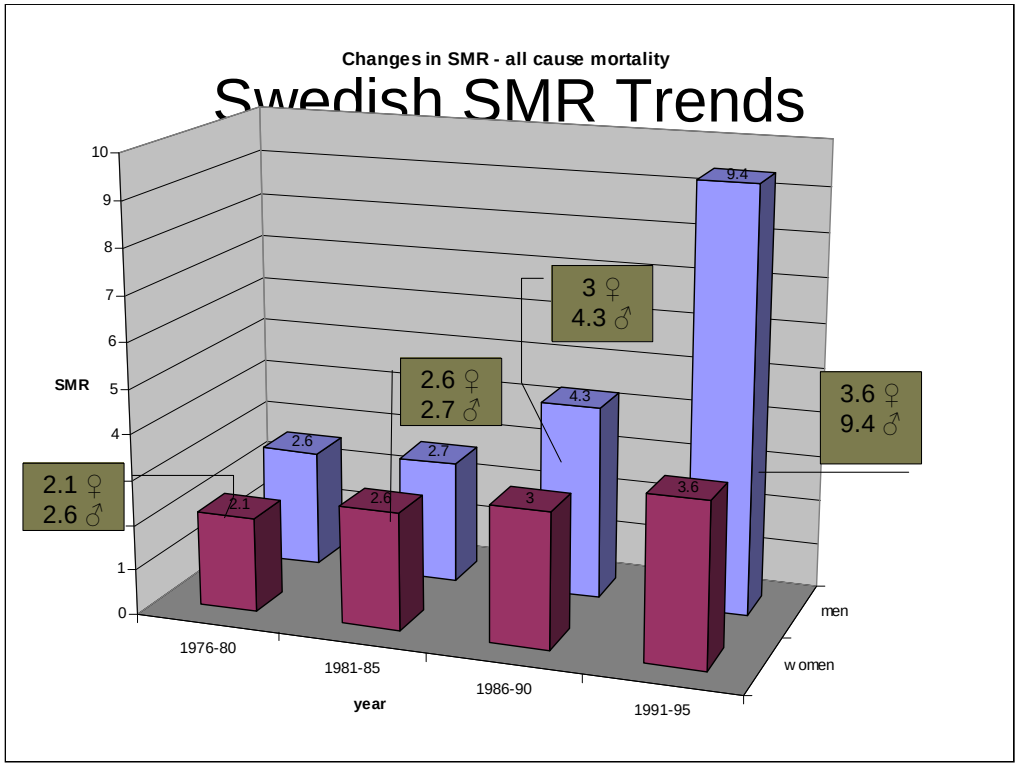
			All causes		Natural		Cardiovascular		Suicide		Unspecified violence	
Year	First admissions	No of deaths	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk
Men												
1976-80	778	196	2.6 (2.2 to 3.0)	1 (reference)*	1.7 (1.4 to 2.1)	1 (reference)†	1.7 (1.2 to 2.2)	1 (reference)†	13.2 (9.8 to 17.5)	1 (reference)*	12.1 (7.4 to 18.6)	1 (reference)
1981-5	761	162	2.7 (2.3 to 3.1)	1.1 (0.9 to 1.4)	1.8 (1.5 to 2.2)	1.1 (0.9 to 1.5)	2.0 (1.4 to 2.7)	1.5 (1.0 to 2.3)	16.9 (12.1 to 22.9)	1.1 (0.7 to 1.7)	12.6 (6.7 to 21.6)	1.1 (0.5 to 2.1)
1986-90	831	104	4.3 (3.5 to 5.2)	1.2 (0.9 to 1.6)	2.0 (1.4 to 2.7)	1.2 (0.9 to 1.8)	4.2 (2.9 to 6.0)	2.9 (1.8 to 4.7)	27.7 (19.9 to 37.6)	1.4 (0.9 to 2.1)	21.1 (11.2 to 36.1)	1.8 (0.9 to 3.5)
1991-5	631	36	9.4 (6.6 to 13.1)	1.7 (1.2 to 2.5)	4.4 (2.3 to 7.4)	2.4 (1.3 to 4.3)	8.3 (3.3 to 17.1)	4.7 (2.1 to 10.4)	47.8 (27.3 to 77.6)	1.6 (0.9 to 2.9)	45.2 (16.6 to 98.4)	3.8 (1.5 to 9.3)
Test for trend				P=0.01		P=0.02		P<0.001		P=0.07		P=0.01
Women												
1976-80	815	259	2.1 (1.9 to 2.4)	1 (reference)*	1.7 (1.5 to 2.0)	1 (reference)†	1.7 (1.4 to 2.1)	1 (reference)*	17.1 (12.2 to 23.3)	1 (reference)*	7.4 (2.7 to 16.0)	1 (reference)*
1981-5	667	176	2.6 (2.2 to 3.0)	1.2 (1.0 to 1.5)	2.0 (1.7 to 2.4)	1.3 (1.0 to 1.6)	2.1 (1.6 to 2.7)	1.3 (0.9 to 1.8)	28.5 (20.0 to 39.5)	1.5 (1.0 to 2.4)	9.9 (2.7 to 16.0)	1.4 (0.4 to 5.0)
1986-90	768	102	3.0 (2.5 to 3.7)	1.2 (1.0 to 1.6)	2.0 (1.5 to 2.6)	1.3 (0.9 to 1.7)	3.1 (2.1 to 4.3)	1.7 (1.1 to 2.6)	35.3 (23.6 to 50.6)	1.5 (0.9 to 2.5)	15.8 (4.3 to 40.4)	2.3 (0.7 to 8.3)
1991-5	551	26	3.6 (2.5 to 5.4)	1.3 (0.8 to 2.0)	2.1 (1.2 to 3.5)	1.3 (0.8 to 2.3)	5.0 (2.1 to 4.3)	2.7 (1.4 to 5.4)	58.6 (29.2 to 104.8)	1.9 (0.9 to 3.9)	20.1 (0.5 to 111.7)	3.4 (0.4 to 28.6)
Test for trend				P=0.05		P=0.04		P=0.002		P=0.04		P=0.13

*Controlling for age at diagnosis and follow up.
†Controlling for age at diagnosis.

Many medical professionals and laypersons have been educated to believe that great progress has occurred in the treatment of patients diagnosed with Serious Mental Illnesses, such as schizophrenia. However, the research evidence suggests otherwise.

One popular research strategy for evaluating the effectiveness of healthcare compares changes in SMRs (standardized mortality ratios) over time. For those who are unfamiliar with the term, the Standardized Mortality Ratio divides the death rate of patients with a certain condition by the death rate of age-matched, unaffected controls.

An interesting analysis performed for residents of Stockholm County (Sweden) evaluated changes in the SMRs of patients diagnosed with schizophrenia between the years 1976 and 1995.



This slide depicts the changes in mortality for Stockholm County patients diagnosed with schizophrenia.

For women, SMRs increased from 2.1 in the period of 1976-1980 to 3.6 in the period 1991 to 1995. [In other words, by 1991-1995, women with schizophrenia were 3.6 times more likely to die than age-matched healthy controls.]

For men, the changes in mortality ratio were even worse. SMRs for males diagnosed with schizophrenia increased steadily from 2.6 in the time period of 1976-1980, to 9.4 in the time period of 1991-1995.

Key Point:

These and other “longitudinal” investigations of mortality rates for patients with Serious Mental Illness have revealed a progressive deterioration of longevity in industrialized nations, despite so-called advances in the quality and delivery of pharmaceuticals.

Public MH patients = 5.9 million per year

Compared to non-SMI, those with SMI:

- die in greater numbers each year
- die earlier than expected
- experience more illnesses than non-SMI

According to the National Association of State Mental Health Program Directors in 2005, almost 6 million people are served by the public mental health system each year.

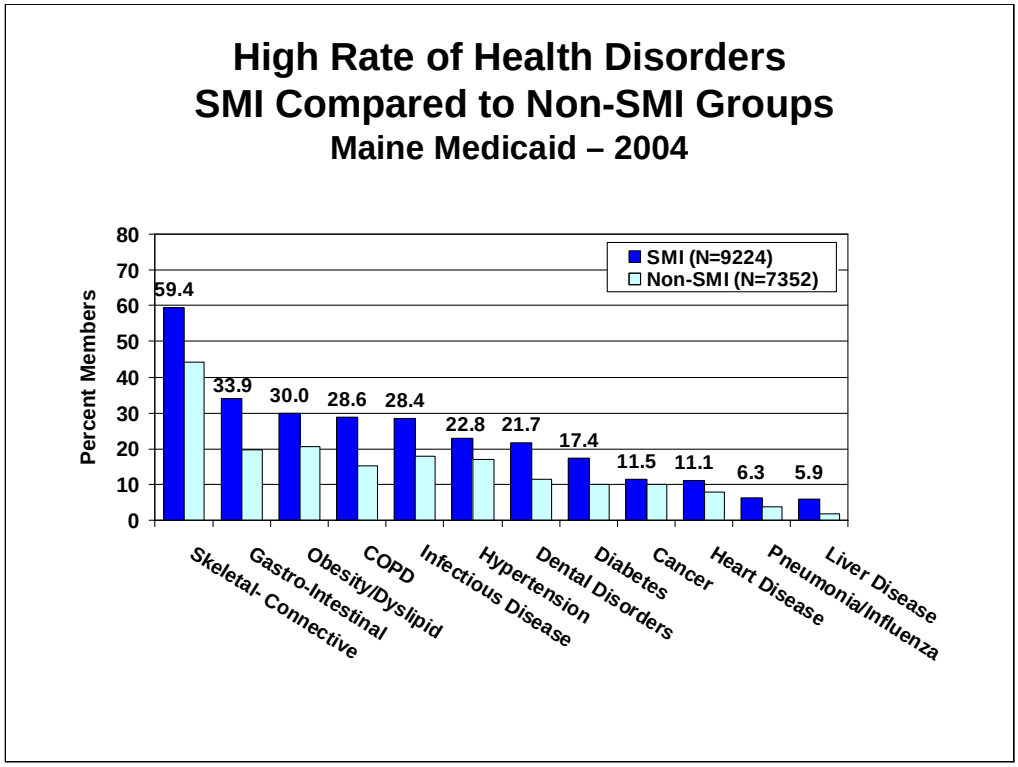
Compared to people without Serious Mental Illness, public health care recipients with SMI:

die in greater numbers each year (1-3.5% vs. 0.5-0.8%)

die 13 to 30 years earlier than expected

and

experience higher rates of somatic (non-mental) disease



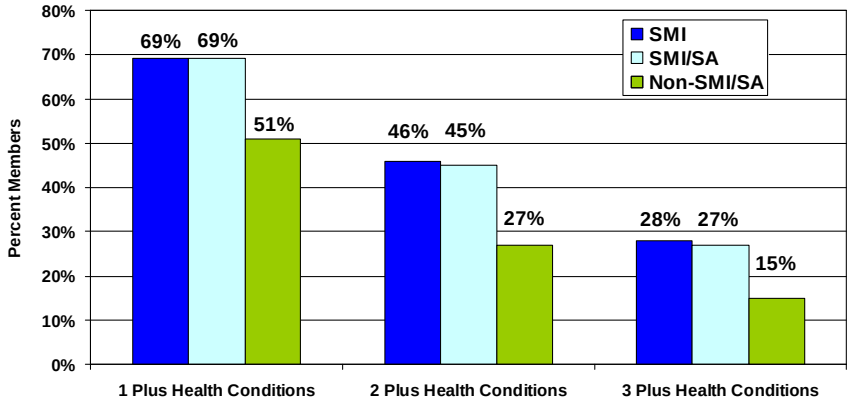
Findings from the state of Maine illustrate the latter problem. Relative to individuals without SMI, Maine Medicaid beneficiaries diagnosed with serious mental health conditions (fiscal year 2004) experienced significantly higher rates of medical illnesses:

	SMI	non-SMI
skeletal	59%	~43%
gastrointestinal	33.9%	~20%
obesity/high lipids	30%	20%
COPD	28.6%	~18%
hypertension	22.8%	~18%
diabetes	17.4%	10%

Sources of data:

Freeman, E. and Yoe, J.T. *The Poor Health Status of Consumers of Mental Healthcare: Behavioral Disorders and Chronic Disease*, Presentation to NASMHPD Medical Directors Work Group, May 2006;Yoe, JT and Freeman, E. (June 19, 2009). The Interdependence of Mental Health and Physical Health. Presented at the SAMHSA National Grantee Conference – Washington, DC; and NRI (summer 2008), "Using Data, Changing Practice."

Burden of Medical Illness: Maine Medicaid 2004



The Maine Medicaid Study also found that patients diagnosed with SMI not only experienced higher rates of specific illnesses, but also experienced higher rates of combined (multiple) and serious diseases.

This slide compares the 2004 prevalence of medical conditions among the Seriously Mentally Ill (SMI with and without substance abuse) vs. non-SMI [Medicaid recipients without mental health conditions or substance abuse]:

	SMI	non-SMI
1 plus conditions	69%	51%
2 plus conditions	46%	27%
3 or more conditions	28%	15%

[Source of data: Freeman, E. and Yoe, J.T., as referenced above.]

Key Point:
Among recipients of Medicaid, SMI is associated with higher rates of physical (somatic) medical disease.

IV. Psychiatric Drug Toxicity

The purpose of this section is to consider the role of medications in the overall disease burden of patients receiving treatment for mental illness.

Psychiatric Drugs ↑ the Odds of Disease

	AD	AP
• Risk of heart disease	↑ 1.4-2x	↑ 2-3x
• Risk of diabetes	unclear	↑ 1.2-7x
• Risk of pneumonia	↑ 1.6x	↑ 1.9x
• Risk of suicidality	↑ 2-15x	unclear
• Risk of stroke	↑ 1.3-1.6x	↑ 1.4-6x
• Risk of dementia	↑ 2-5x	↑ 2-14x

This slide depicts the “odds” (likelihood) of developing heart disease, diabetes, pneumonia, suicide, stroke, or dementia for mentally ill patients based upon exposure to **antidepressant (AD)** or **antipsychotic (AP)** drugs.

Numerous investigations, performed in a variety of age groups, have demonstrated the potential of pharmaceuticals to accelerate the risks of disease and death. Even when compared to similarly diagnosed patients who have avoided antidepressant or antipsychotic drugs, consumers of these medications have been two to fifteen times more likely to attempt or complete suicide, and two to seven times more likely to develop pneumonia, diabetes, heart disease, or stroke.

Equally important -- but seldom discussed by health care professionals – the use of antidepressant or antipsychotic drugs has been repeatedly associated with a two- to fourteen-fold higher likelihood of dementia.

Dementia defined:

- From Latin *de mens / de mentis*

out of (away from) one's mind

The word "dementia" is derived from the Latin terms

de mens / de mentis

meaning "**out of (or away from) one's mind"**

Features of Dementia

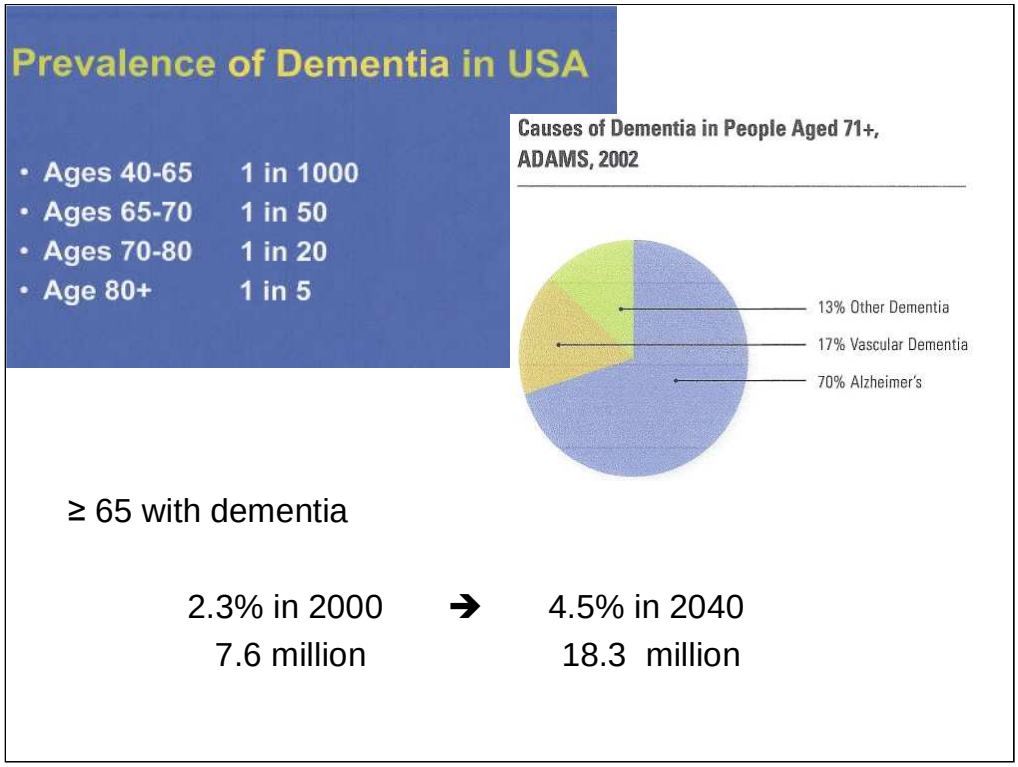
- ❖ Memory impairment
- Aphasia (impaired language)
- Apraxia (impaired ability to carry out motor activities)
- Agnosia (failure to recognize objects)
- Executive functioning deficits

  planning, organizing, sequencing, abstracting

In performing their clinical duties, American psychiatrists are trained to use a specific classification system known as the *Diagnostic and Statistical Manual of Mental Disorders* (aka, the *DSM*). According to the most recent editions of this manaul, the defining feature of dementia is the impairment of memory.

It is important to appreciate the fact that other specialists in medicine approach this topic more methodically. To neurologists, for example, dementia is not a disease, per se. Rather, the term dementia refers to a syndrome of signs and symptoms – such as deficits in thinking, perceiving, feeling, moving, speaking, writing, or planning – which are caused either by toxins, by disease processes outside the brain (e.g., diabetes, hypothyroidism, cancer), or by degenerative conditions which originate in the central nervous system (e.g., Parkinson's disease, Pick's disease, Creutzfeld-Jakob disease, multiple sclerosis).

Key Points:
Dementia is arguably under-recognized by psychiatrists in the United States for at least three reasons: 1) due to the inordinate emphasis which the *DSM* has placed upon the loss of memory; 2) due to a sociocultural expectation that dementia should appear only in old age; and 3) due to the tendency of physicians to attribute dementia-symptoms in psychiatric patients to mental illness, rather than to toxins or somatic (bodily) disease.



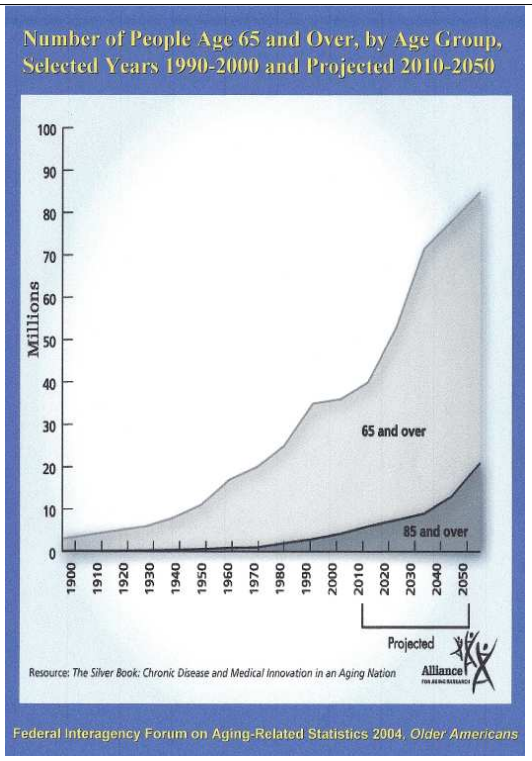
In the year 2000, the prevalence of dementia among Americans age 65 or older was 7.6 million people – roughly 2.3% of the entire U.S. population. This number is projected to increase to 4.5% of the U.S. population by the year 2040 (18.3 million people).

The box on the left depicts the age-related rates of dementia:

ages 40-65	0.1% of this group will be diagnosed with dementia
ages 65-70	2% of this group will be diagnosed with dementia
age 70-80	5% of this group will be diagnosed with dementia
80+	20% of this group will be diagnosed with dementia

The pie chart on the right depicts the prevalence of the major diseases which give rise to dementia:

70% of dementias are associated with Alzheimer's disease
17% of dementias are associated with vascular disease (e.g., stroke)
13% of dementias are associated with other medical conditions



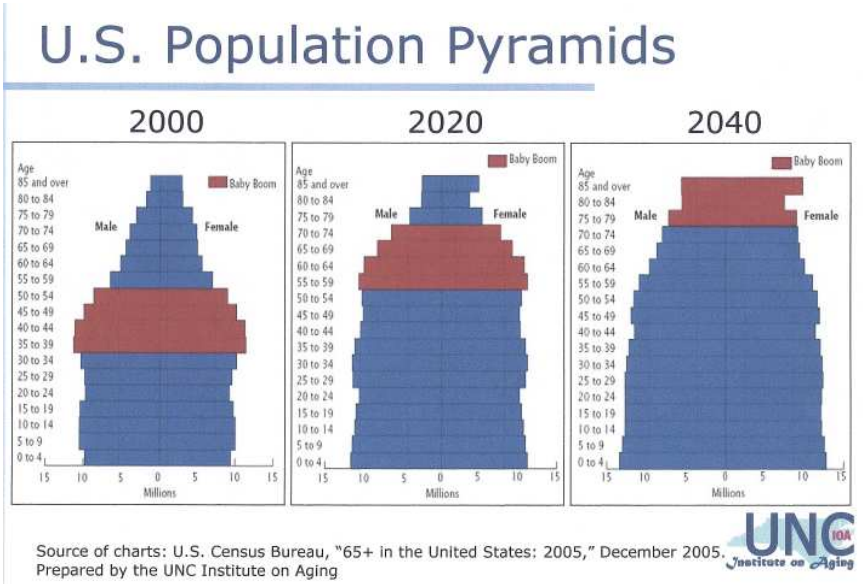
This slide depicts the number of people in the U.S. population of retirement age (light gray: 65 and above; dark gray: 85 and above).

In the early 1900s, the U.S.A. was populated by a relatively small number of older people. This situation changed drastically after 1920:

# of U.S. residents aged 65 or older	
1900	3.1 million people
1920	4.9 million people
1940	9 million people
1960	16.7 million people
1980	25.7 million people
1990	31.2 million people
2000	35 million people

≥ 65 years of age

12% to 18% to 21%



With the end of World War II came the return of soldiers to the U.S. mainland, and with their return came an explosion in the birth of babies. The so-called "Baby Boom Generation" refers to this population subgroup whose members were born between 1945 and 1964.

As the "Baby Boomers" approach their retirement years (red bars in the slides above), the overall structure of the U.S. population will change from a pyramid shape (2000) to a rectangle shape (2040) – a phenomenon which some researchers have called "The Squaring of the Population Pyramid."

These demographic shifts have important implications for economic and healthcare policy, because the number of retirees (aged 65 and older) will reach an historical high point:

12% of the population in 2000

18% of the population in 2020

21% of the population in 2040

Drug Induced Dementia

DSM-IV, Text Revision (2000)
Substance-Induced Persisting Dementia

"*Features are those associated with dementias generally…can occur in association with…alcohol, sedatives, hypnotics and anxiolytics, or other or unknown substances*…"

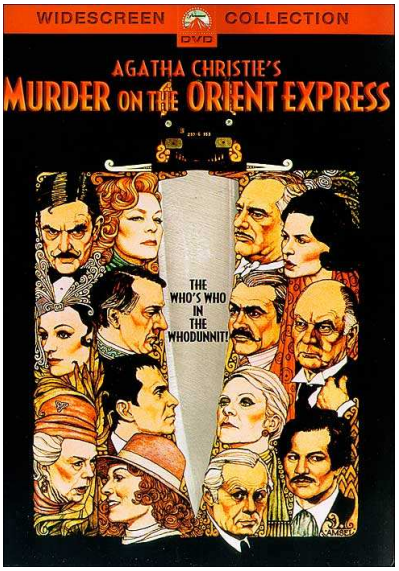
Given the fact that the prevalence and costs of dementia are expected to rise in conjunction with America's changing demographics, there is an urgent need for health care providers and policy makers to prevent the fundamental causes of brain disease.

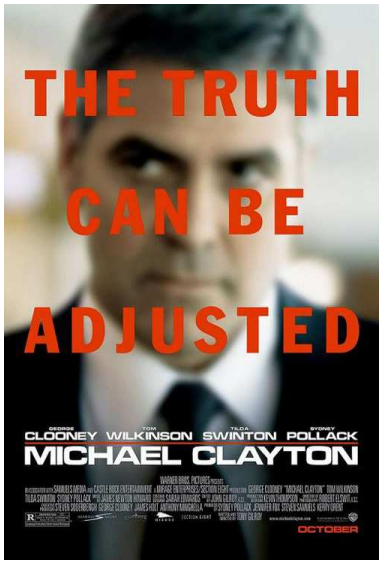
It is within this context that many health care providers will need to revise their approach to medicating patients.

Even though the construct is seldom mentioned by physicians in their clinical work, it is nevertheless significant that the American Psychiatric Association's own diagnostic handbook (the *DSM*) has long recognized the fact that ***drugs of any kind*** may induce or enhance long-lasting, cognitive limitations.

To the extent that psychopharmaceuticals contribute to brain dysfunction and dementia (i.e., substance-induced persisting dementia), they are perpetrators of a perfect crime.

A perfect crime…





In the novel, *Murder on the Orient Express* – Agatha Christie's famous fictional detective, Hercule Poirot, must determine the identity of the person who has killed a fellow train passenger. The case is never definitively solved because there are twelve different suspects for the murder, each of whom has strong motives for the crime.

Like the *Murder on the Orient Express*, physicians overlook drugs as a cause of dementia because they usually focus upon other risk factors [when there are multiple suspects, some or all of them go free].

In the Academy Award winning film, *Michael Clayton*, an attorney who represents a large chemical company becomes a whistle blower after he discovers that his client has knowingly concealed the deadly effects of a farm product. In an act of corporate retaliation, the attorney is cleverly killed by hit men so that his death appears to be a suicide.

Like the murder in *Michael Clayton*, drug-induced dementia in psychiatry is a "perfect crime" [no one suspects the drugs as the cause of dementia, because cognitive and behavioral deficits are blamed on the patient's "pre-existing" mental health condition].

Antipsychotic Timeline

*timeline = year that the drug was invented or first used

1st generation drugs 1950 to 1960s

Thorazine, Haldol, *Clozaril

2nd generation drugs 1970 to 1990s

Risperdal, Zyprexa, Seroquel, Geodon

3rd generation drugs 2000 to 2010

Abilify

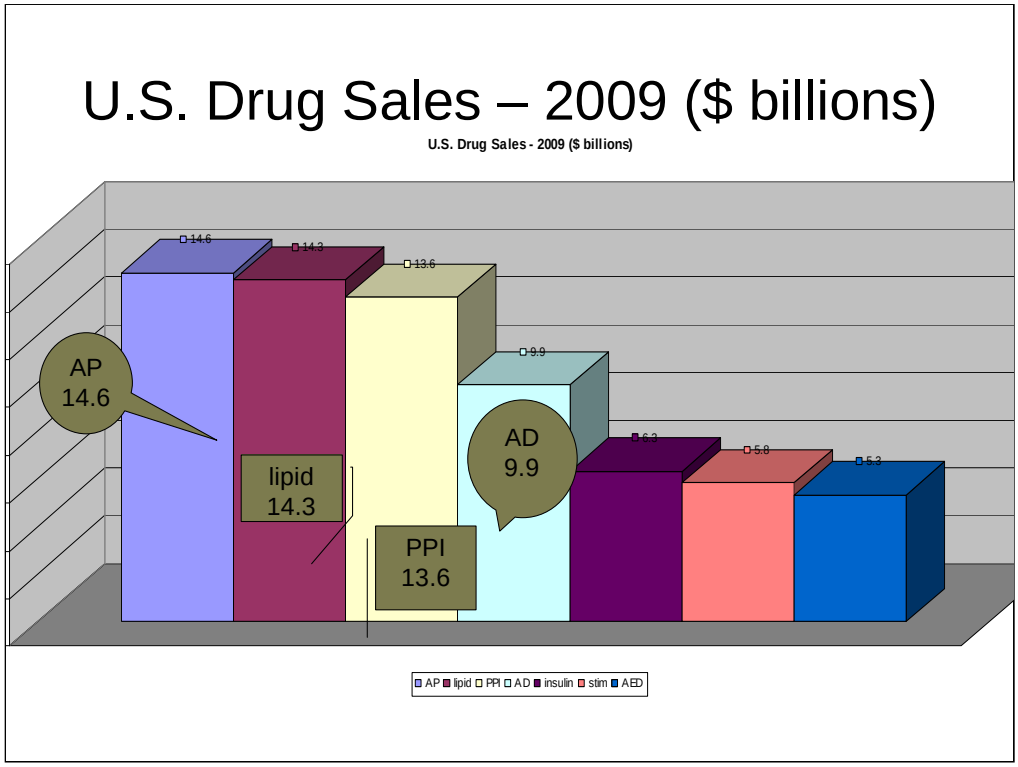
*Invented in 1958, clozapine was introduced in Europe in the early 1960s. It did not gain FDA approval in the U.S.A. until 1989. Partly for this reason, American physicians refer to it as a "second generation" drug.

Recall from slide #13 that antipsychotics were the top selling drugs in the United States in 2009 (14.6 billion dollars). The history of antipsychotic drugs dates back to the early 1950s when physicians in France hypothesized that sedating chemicals might be valuable in "taming" the residents of the world's asylums.

There are two major ways of describing the evolution of antipsychotic drugs. As shown above, it is possible to describe this history in terms of "when" the drugs entered clinical use. A second method refers to the molecular and physiological effects of each agent.

According to this latter approach, the "first" generation drugs (typical or conventional antipsychotics) are associated with the blockade of dopamine receptors and specific kinds of adverse effects. The so-called "second" generation drugs (atypical antipsychotics) are distinguished by the blockade of dopamine and serotonin receptors, along with an "allegedly" more benign side effect profile. The so-called "third generation" drugs (such as Abilify) is characterized by its affinity for specific states of the dopamine receptor (partial agonism).

Unfortunately, the myth of "atypicality" has not held up. Many consumers of 2nd and 3rd generation drugs have developed Parkinson's disease, tardive dyskinesia, and diabetes. Astute clinicians have openly questioned the classification of the newer products, such as Risperdal (risperidone), after finding that recommended doses have induced toxicities identical to those which are commonly inflicted by the older drugs.



The point of this slide is to reinforce an impending public health disaster.

As antipsychotic drugs are promoted and used for an increasingly broad array of non-psychotic conditions – such as depression, autism, irritability, hyperactivity, insomnia, addiction, and pain – it is remarkable that physicians collude in an escalating pattern of drug use.

The fact that the top-selling drugs in America in 2009 are the same chemicals which elevate the risks of dementia, heart attack, stroke, diabetes, and early death is a fact which too many health care providers and policy makers ignore, minimize, or deny.

Top Drug Sales in 2009 in US $

antipsychotic drugs	14.6 billion dollars
lipid regulators (drugs used for high cholesterol)	14.3 billion dollars
proton pump inhibitors (drugs used for acid reflux)	13.6 billion dollars
antidepressants	9.9 billion dollars
insulin	6.3 billion dollars

Dept. of Veterans Affairs

Kales et al (2007)

23,436 patients (national database)

≥ 65 years of age

diagnosis of dementia in 2002 or 2003

12-month mortality risk after starting a psychiatric drug

In 2007, investigators affiliated with the Department of Veterans Affairs reported the 12-month mortality rates for all retired veterans who received a diagnosis of dementia in fiscal year 2002 or 2003.

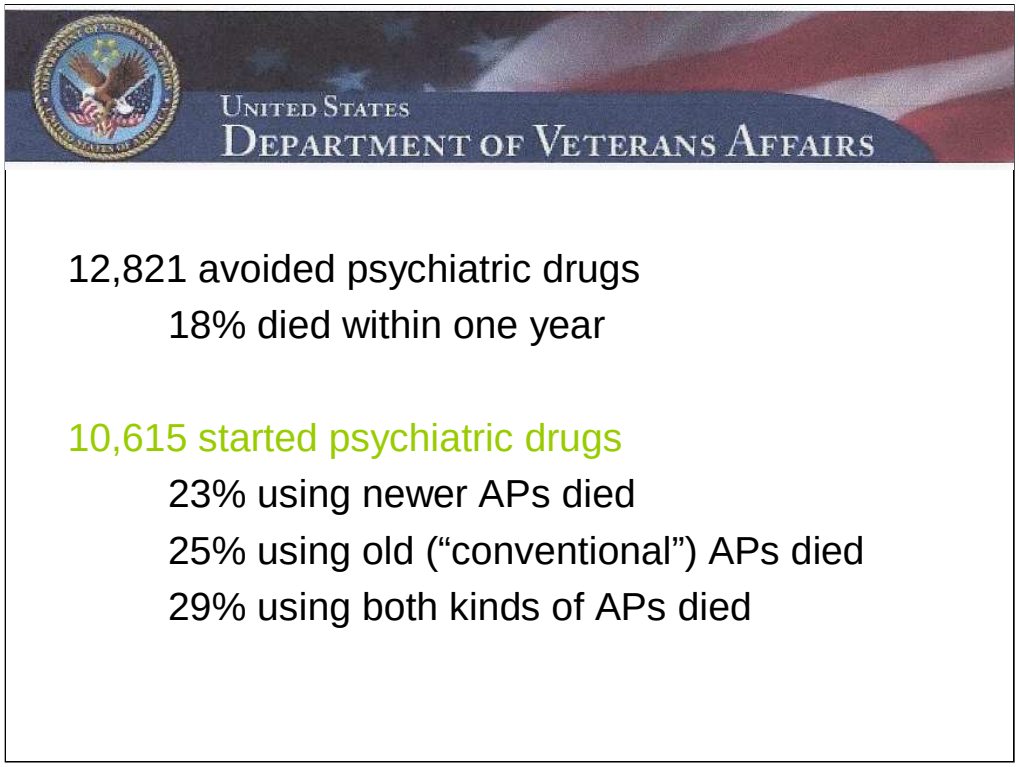
Study design:
The study identified dementia patients from a national database of veterans (23,436 individuals) who were 65 years of age or older.

Excluded from the investigation:

any patient who had used psychiatric drugs in the 6 months preceding the diagnosis of dementia

any patient who had previous or new diagnoses of a seizure disorder

any patient who received treatment with lithium



The research team compared the death rates of demented veterans based upon new outpatient exposures to various classes of psychiatric drugs.

Of the 12,821 patients who avoided exposure to psychiatric drugs, 18% died within one year.

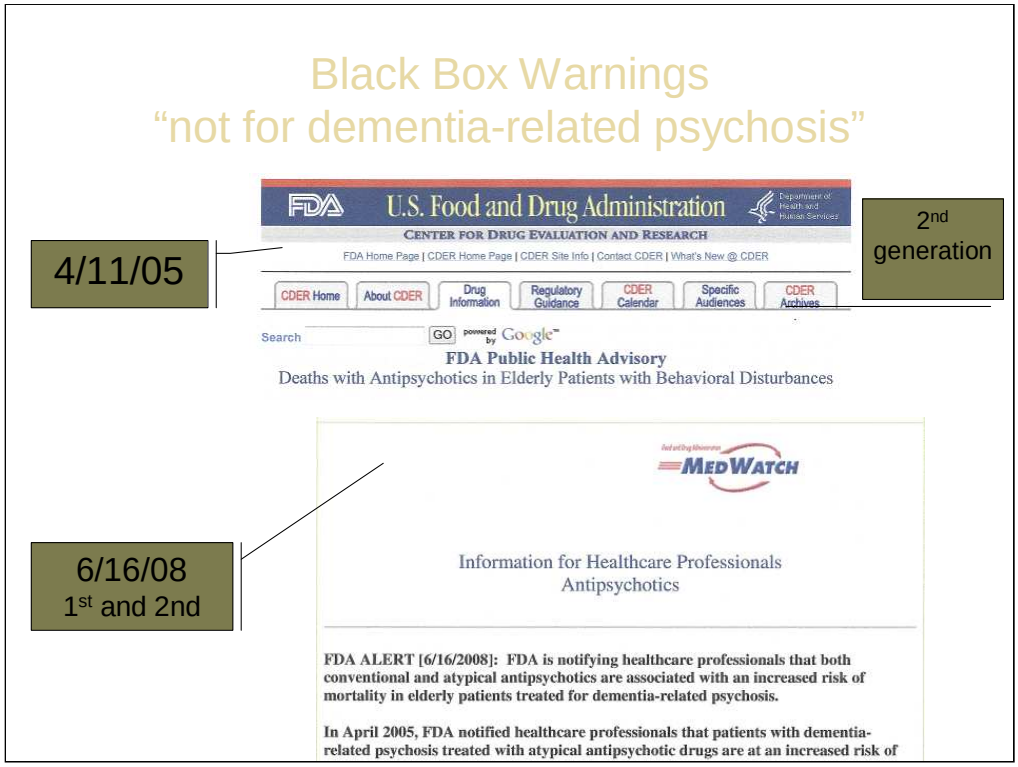
Of the 10,615 patients who experienced treatment with antipsychotic drugs, death rates were consistently higher:

23% exposed to newer "atypical" antipsychotics died within 1 year

25% exposed to older antipsychotics died within 1 year

29% exposed to both (sequentially or concurrently) died within 1 year

Other folks started to notice the same trend in different patients…



On April 11, 2005, the Food and Drug Administration issued a Public Health Advisory to inform healthcare professionals about a 1.6 to 1.7x higher risk of mortality for elderly demented patients following exposure to the "2nd generation" antipsychotic drugs. This alert reflected the detection of higher death rates – mostly cardiac or pulmonary – in the FDA's "Randomized Controlled Trial" database for olanzapine (Zyprexa), risperidone (Rispderdal), and quetiapine (Seroquel).

Two years later, this warning was revised and expanded because of further research discoveries. On June 16, 2008, the FDA alerted physicians that the risk of premature death in elderly demented patients was elevated by both the "new" and "old" (1st generation) antipsychotic drugs.

In England, some physicians began to wonder ---

what would happen to dementia patients if they stopped taking antipsychotic drugs ?

U.K.- DART-AD
Dementia AP Reduction Trial

Enrolled residents of nursing or residential homes in four areas (2001-2004); followed patients to April 2006

All patients had been diagnosed with possible or probable Alzheimer's and all had taken APs for ≥ 3 months (APs = risperidone, thioridazine, haloperidol, trifluoperazine, or chlorpromazine)

Mean duration of drug use: 25 months

In 2009, Ballard et al reported the results of the Dementia Antipsychotic Reduction Trial (DART-AD) – a novel study performed among dementia patients in four different regions of the U.K.

At the time of entry into the study, all of the patients had been diagnosed with possible or probable Alzheimer's disease, and all of them had consumed an antipsychotic drug for at least three months.

Mean duration of drug use: 25 months

DART-AD
Ballard et al (2009)

- 165 patients were randomly assigned to antipsychotic (83) or placebo (82)
- Assessed patients according to treatment fidelity (compliance) and outcome…
- Primary outcome: 12-month mortality

Study design:
The researchers randomly assigned 165 patients to two groups: in one group, 83 patients were continued on antipsychotic drug therapy; in the second group, 82 patients were switched to placebo (inert pill).

The investigators carefully monitored the patients for compliance with the new treatments.

Primary outcome: 1-year mortality

Outcomes Based Upon Continuing Use of Drugs vs. Placebo

	APs	PBO
% surviving		
1 year	75%	79%
2 year	46%	71%
3 year	30%	59%
3 ½ years	26%	53%

APs = antipsychotic drugs
PBO = placebo

Researchers were able to compare outcomes (mortality and survival rates) over a follow-up period of 1 to 3 ½ years.

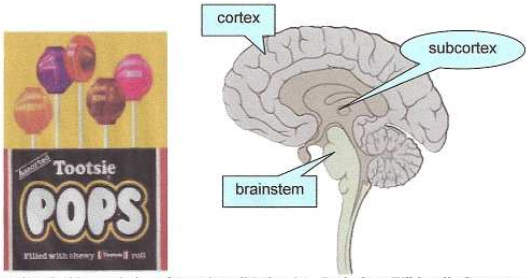
Regardless of the duration of follow-up, the highest mortality rates occurred among the chronic users of antipsychotics: 25% were dead within 1 year, 74% were dead within 3 ½ years.

In contrast, the cessation of antipsychotic drug therapy was associated with significantly higher rates of survival: 79% surviving at 1 year, 47% surviving after 3 ½ years.

Key Point:
The withdrawal of antipsychotic drug therapy from demented patients was associated with significantly higher rates of extended survival.

Antipsychotic drugs are deadly for dementia patients…

- what about giving them to the non-demented ?



Tootsie Pops reproduced with permission of Tootsie Roll Industries. Brain from Wikimedia Commons.

candy coating	=	**cortex**
tootsie roll center	=	**subcortex**
lollipop stick	=	**brainstem**

name		location	functions
the cortex	=	outer (or top) layer	"human" functions planning, intending, meaning
the subcortex	=	middle layer	"animal" functions appetite, sex, emotions
the brainstem	=	base layer	"vegetative" functions sleep/wake, breathing, heart beat

In order to appreciate the effects of chemicals upon the human brain, it is important to understand the structure of that remarkable organ. As a method of simplifying the anatomy for the non-scientist or layperson, it may be helpful to think about the brain in comparison to a Tootsie Roll Lollipop. Just as the lollipop has three discrete sections (an outside candy coating, a chocolate center, and a stick), the human brain can be divided into three sections (shown above).

Historically, scientists have attributed different functions to these various brain zones:

cortex	uniquely human functions of higher thought/planning/creating
subcortex	animal functions (appetite, sex, emotions)
brainstem	vegetative functions (asleep/awake, breathing, heart beat)

As the theme of this presentation is dementia, it is important to appreciate the fact that dementia can result from serious injury to any one of the three zones described above.

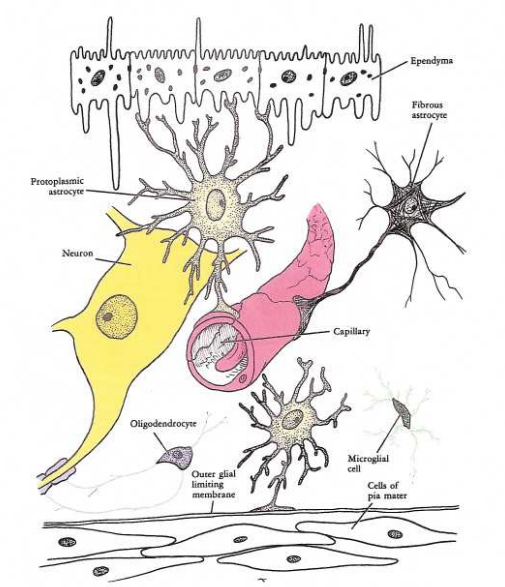
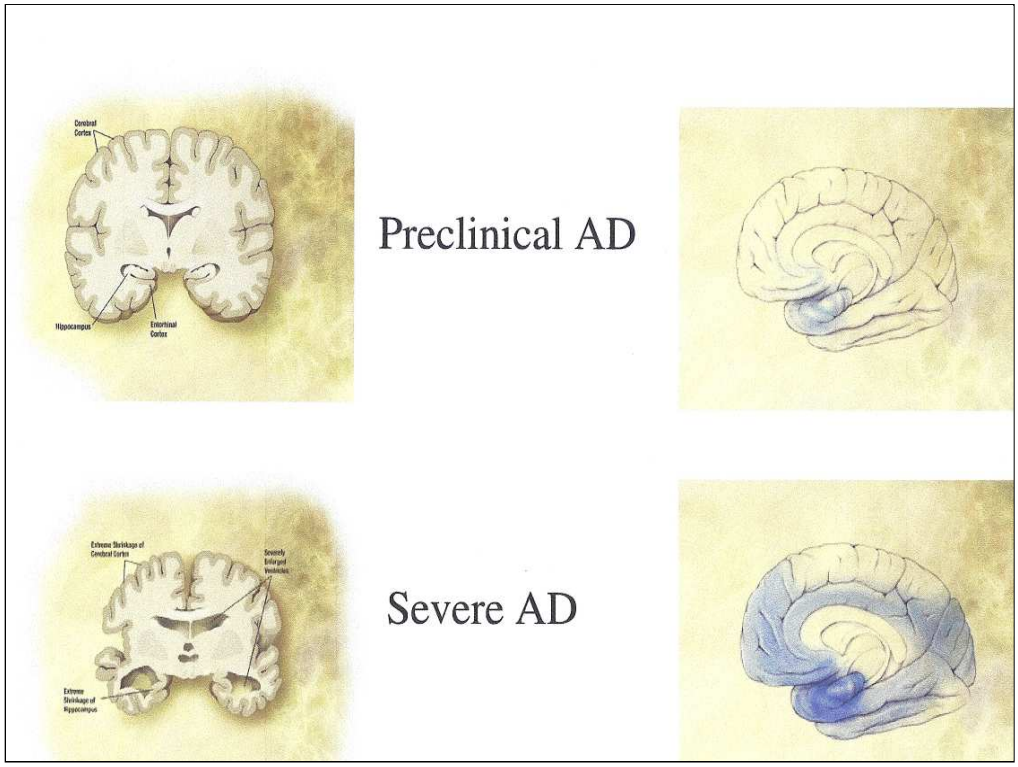


FIGURE 3-1 A diagrammatic representation of the arrangement of different types of neuroglial cells.

When the human brain is examined under a microscope, it is possible to detect two basic types of cells. These are known as **neurons** and **glia**.

Neurons (shown here in yellow) have traditionally been regarded as the key actors which control brain activity. In contrast, glia (shown above in black, gray, and tan) have traditionally been relegated to secondary roles, such as nourishment and infection response. [Interestingly, these concepts are now overly simplistic and outdated].

For the purpose of this lecture, it will suffice to appreciate the fact that human behavior and intelligence depend upon the proper functioning and survival of neurons. **In fact, the death of neurons is a common feature of all disease processes which result in dementia.**

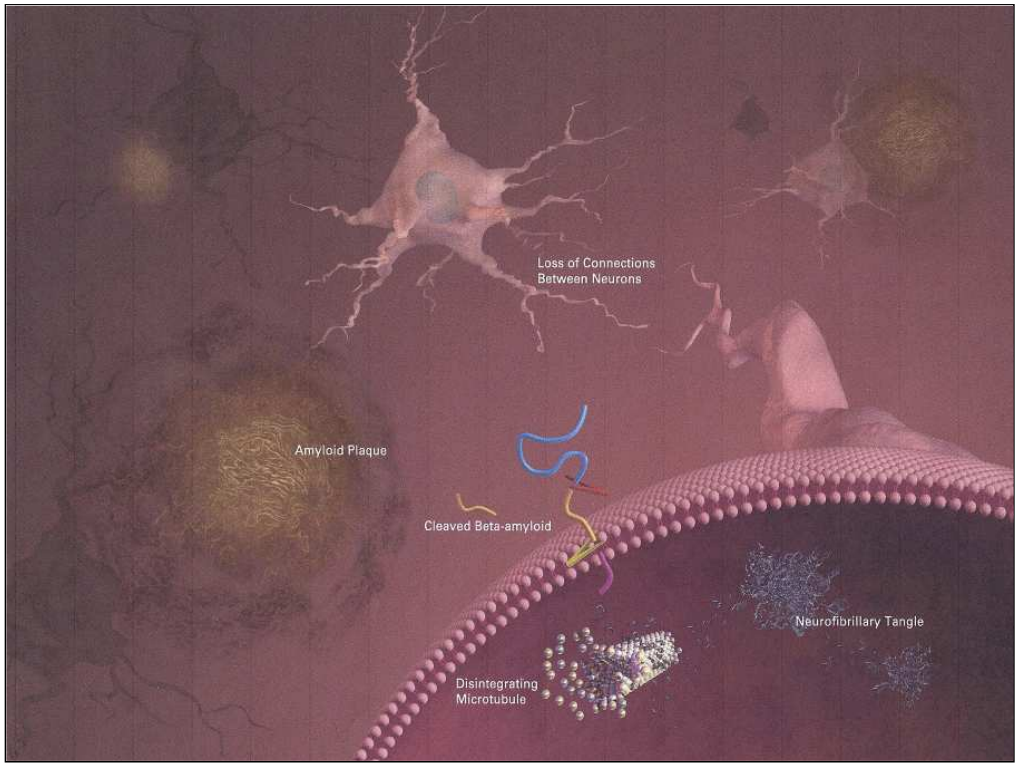


Recall from slide #38 that 70% of all dementias in the U.S.A. are attributed to Alzheimer's disease (AD).

These pictures show the locations of abnormal tissue in the human brain as Alzheimer's disease begins (top) and progresses (bottom).

Top: pathology begins within the hippocampus of the temporal lobe

Bottom: in advanced disease, Alzheimer's pathology extends well beyond the temporal lobe. The hippocampus undergoes profound degeneration. Fluid-filled spaces of the brain (known as ventricles) become enlarged.



The defining features of Alzheimer's disease include (but are not limited to):

1) abnormal deposits inside neurons (composed of a protein known as "tau", these are sometimes referred to as **neurofibrillary tangles**]

2) abnormal deposits outside neurons (composed of a protein known a beta-amyloid, these deposits are referred to as **amyloid plaques**)

3) the disintegration and death of neurons

This slide depicts Alzheimer's abnormalities as they would appear through the lens of a microscope. The pink cells (top center, lower right) are neurons. An amyloid plaque can be seen in the lower left. Tau tangles appear inside the large neuron (dark blue). Disintegrating cell parts (microtubules) appear in white.

How Do Doctors Diagnose Alzheimer's Disease?

No way to know for sure while a patient is still living…

1) look at symptoms and how they evolve
2) "biomarkers" are in development
3) gold standard = autopsy pathology

Because dementia is a syndrome which arises from many possible medical conditions, doctors must work methodically to identify the root cause of a patient's cognitive and behavioral limitations.

Even though the structural features of Alzheimer's disease have been recognized for many decades, there remains no definitive way to confirm the presence of these changes in living patients. Since brain samples (biopsies) are not generally obtained for this purpose -- due to the fact that brain surgery is invasive, expensive, and potentially hazardous – physicians render the diagnosis of Alzheimer's by evaluating the quality and progression of symptoms, and by ruling out other potential causes of disablity.

Many researchers are now working to identify "biomarkers" which will permit the accurate determination of Alzheimer's disease, based upon non-invasive tests of biological samples (blood, urine, cerebrospinal fluid) or via brain scan techniques. For now, however, the gold standard for determining Alzheimer's disease remains the postmortem examination of brain tissue – otherwise known as autopsy.

Postmortem Pathology

Do Antipsychotic Drugs Cause Alzheimer's Disease ?

If they do, we should expect to see evidence of Alzheimer's pathology (abnormal anatomy) among patients who have received antipsychotic drugs…

Postmortem Studies of Humans

1988 Buhl and Bojsen-Moller – 100 patients (consecutive autopsies)

schizophrenia	35% Alz. pathology
non-psych controls	0% Alz. pathology

1989 Soustek – 225 pts with chronic schizophrenia (dying in 1975-85)

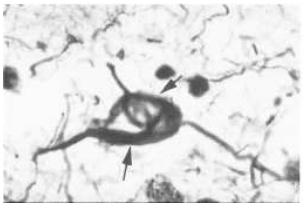
41% showed Alz. pathology
6x higher rate than general population

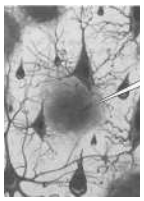
1994 Wisniewski – 102 patients with history of schizophrenia

41 died prior to antipsychotic era	46% had tangles
62 died after antipsychotic era	74% had tangles

Historically, pathologists have devised a variety of chemical methods for preserving and examining brain tissue. Accompanying these changes have been several revisions in the classification schemes (thresholds) used to decide if a specimen demonstrates “probable” vs. “definite” signs of Alzheimer’s disease.

In light of the complexity of these revisions, there is a compelling record in the medical literature which suggests a positive association between antipsychotic drugs and the appearance of Alzheimer’s pathology within the human brain.





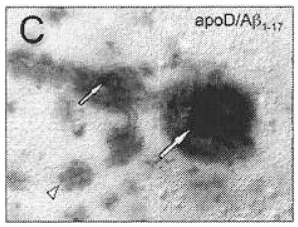
2002 Bozikas – 18 schizophrenia patients vs. 14 age-matched controls
- patients had 400% ↑ tangle density in cortex (layer II of EC)
- patients had ↑ plaque density (throughout the brain)

2005 Ballard et al – studied 40 patients with Lewy body dementia
- 23 patients avoided antipsychotic drugs
- 17 patients received antipsychotics
  - when compared to the other patients, the 17 drug-consumers exhibited:
    - 30% higher density of cortical plaques
    - 65-367% higher density of tangles

apoD is marker of neuropathology

University of Pittsburgh (Desai et al, 2005)

apoD is key a feature of Alzheimer's disease
63% of the beta-amyloid plaques contained apoD



If antipsychotic drugs are causally related to Alzheimer's pathology, it would be important for medical doctors and researchers to discern which anatomic abnormalities they potentially induce.

It is in this context that a recent discovery in neuroscience is most pertinent. Using electron microscopy to investigate the smallest components of brain cells, a team of investigators at the University of Pittsburgh (Desai et al, 2005) identified apolipoprotein D as a core component within the beta-amyloid deposits (plaques) which distinguish Alzheimer's disease.

Thomas et al (2001)
autopsy study of brain levels of apoD (ug/mg)

	schiz n=20		bipolar n=8		controls n=19
% using APs	90% (18)	75% (6)		0	
DLPFC	0.244		0.233		0.115
caudate	0.132		0.112		0.059

apoD levels were 2X higher in users of APs

APs = antipsychotic drugs (1st generation and clozapine)

In a postmortem investigation of psychiatric patients who had received treatment with various kinds of antipsychotic drugs, researchers evaluated the levels of apoD in two different regions of the brain.

Brain Region	Tootsie Pop Equivalent
DLPFC = dorsolateral prefrontal cortex	candy coating
caudate = region of the subcortex	tootsie roll center

Study Design:
The study compared two groups of medicated subjects (20 diagnosed with schizophrenia, 8 diagnosed with bipolar disorder) and one group of mentally healthy controls. 75-90% of the psychiatric patients had received treatment with antipsychotic drugs, consisting of 1st generation drugs or clozapine.

When compared to drug-naive controls, patients exposed to antipsychotics had apoD levels that were two times higher in the cortical and subcortical zones of the brain.

apoD in Animals

mice and rats (multiple investigations) >>

14 to 45 days of OLZ, RISP, or CLZ

all three drugs resulted in higher mRNA and higher protein levels of apoD in cortical and subcortical regions of brain

mRNA = messenger RNA (a molecular precursor for protein synthesis)

Similar investigations have been performed in non-human animals. In studies involving mice and rats, exposures to clinically relevant doses of antipsychotic drugs (olanzapine, risperidone, or clozapine) have resulted in higher protein levels of apoD in the cortical and subcortical regions of the brain.

Key Point:
To reiterate, the relevance of this finding pertains to the fact that apoD is a core component of the amyloid plaques which are found in Alzheimer's disease.

Other Postmortem Studies
rabbits, rats, monkeys, guinea pigs

1958 – 1975

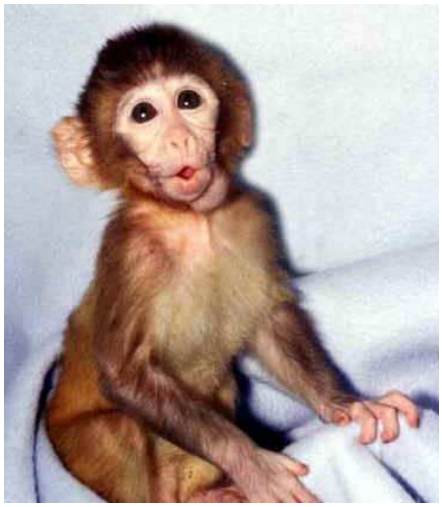
all showed damage to cortex, subcortex, and brainstem following brief (2 wks) or chronic exposure (up to 1 yr)

Recall that one of the key features of Alzheimer's disease and other diseases which cause dementia is the death and disintegration of brain cells.

The purpose of this slide is to call attention to the existence of more than a dozen early experiments in lab animals which were performed between the late 1950s and 1975. Common to all of these investigations of drug effects were the discoveries that brief (2 week) and extended (up to 1 year) exposures to the first-generation antipsychotics resulted in diffuse damage throughout the brain.

Regrettably, textbooks of medicine and medical training programs have excluded this legacy. For professionals and laypersons who are interested in this well concealed history, the publications of the Austrian neuropathologist, Dr. Kurt Jellinger, are invaluable.

University of Pittsburgh
(2005, 2007, 2008)



Do lab techniques (specimen processing) affect the structure of the brain?

As an aside:
What about drugs?

The fact that the first-generation drugs were diffusely neurotoxic was not regarded as a problem when antipsychotics arrived on the market in the 1950s. Ironically, the destructive capacity of these pharmaceuticals was initially celebrated as a necessary component of drug therapy, because psychiatrists mistakenly believed that psychosis could be “cured” via chemical lobotomy.

Unfortunately, many physicians who practice medicine today may not appreciate the continuing evidence from animal experiments which has revealed the potential of old and new drugs to destroy the brain.

In this context, a recent series of publications prepared by scientists at the University of Pittsburgh have produced dramatic results. Motivated by a desire to understand the cellular effects of lab techniques (do the sequential steps involved in the preparation or storage of brain tissue alter the tissue in any way), the investigators made several vital discoveries.

Experiment

18 adult male macaques (4.5 to 5.3 yrs old)

oral doses of haloperidol or placebo (27 months)
oral doses of olanzapine (17 months)

relevant doses of drugs vis-à-vis human therapy
1-1.5 ng/mL for HAL
10-25 ng/mL for OLZ

Study Design:
The experiment exposed 18 adult male macaques (4.5 to 5.3 years of age) to clinically relevant, oral doses of haloperidol (Haldol), olanzapine (Zyprexa), or placebo (sucrose pellets).

Animals received treatment for approximately 1.5 to 2 years.

Medications were administered once a day, in order to produce serum drug levels equivalent to those which occur in human patients at clinically recommended doses.

At the end of the experiment, the animals were sacrificed. The brains of the medicated animals were compared to the brains of the drug-free controls.

Changes in Behavior and Brain

4 of 6 monkeys on OLZ >> aggressive
2 of 6 monkeys on HAL >> aggressive

atrophy of cortex/cerebellum/brainstem

HAL	9% lower volume of brain 9% decreased brain weight
OLZ	10.5% lower volume of brain 11% decreased brain weight

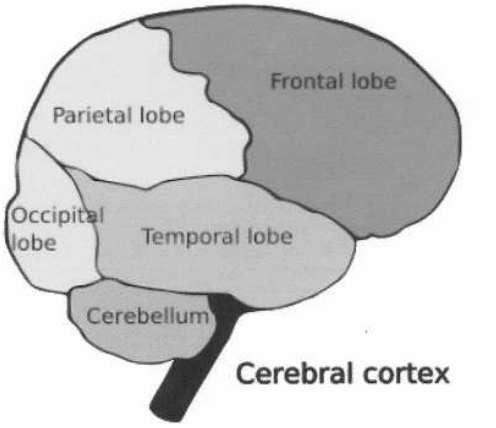
Several important behavioral and anatomical effects were observed.

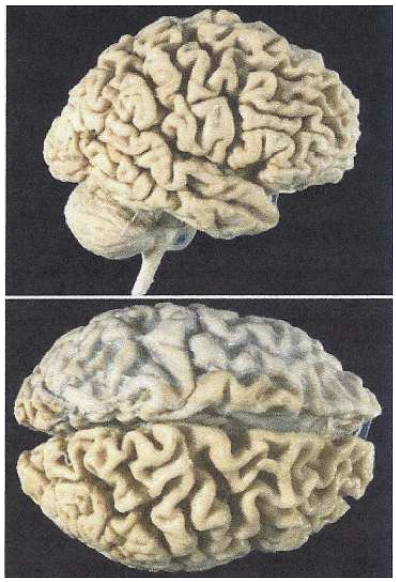
First, all of the animals appeared to develop an aversion to the taste and/or subjective effects of the medications.

Second, a significant number of monkeys became aggressive during the study (2/3 of the olanzapine recipients, 1/3 of the haloperidol recipients).

Third, chronic exposure to haloperidol and olanzapine resulted in comparable and diffuse reductions in brain volume and brain weight.

f/u Studies of Parietal Lobe





Curious to know why the monkey brains had become progressively smaller in weight and volume, the Pittsburgh scientists conducted several follow-up investigations.

In the next studies, they performed meticulous inspections of brain tissue, focusing upon changes in the **parietal lobe**.

Brain region	Tootsie Roll lollipop equivalent
parietal lobe = cortical region	candy coating

The slide above demonstrates the comparable region as it appears in the human brain.

Parietal Lobe Cell Loss

Reductions in Cell Number After Drug Treatment

	haloperidol	olanzapine
total cells	10.6%	7.4%
neurons	6.3%	5.5%
oligodendrocytes	13.9%	11.8%
astrocytes	20.4%	20.5%

Using a computer-assisted counting technique (known as stereological assessment), the researchers compared the numbers of discrete brain cell populations in the medicated vs. unmedicated monkeys.

Both of the antipsychotic drugs resulted in the loss of brain cells from the parietal lobe. More specifically, the numbers of neurons and glia (astrocytes and oligodendrocytes) were all significantly reduced.

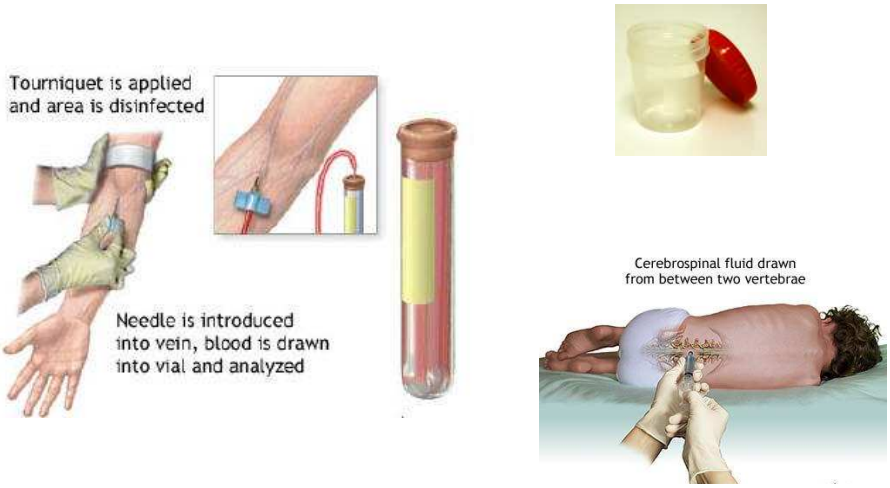
Review of Brain Cells

neuron = a nerve cell that makes, absorbs, stores, and releases chemicals

oligodendrocyte = a type of glial cell which produces myelin, the lipid-containing insulation layer which surrounds neurons and enhances the speed of cell-to-cell communication

astrocyte = a type of glial cell which performs many functions, including the synthesis, release, and reuptake of brain chemicals; and the provision of structural support, detoxification, nourishment, and “housekeeping” functions (clearing away dead or waste material)

Biomarkers in Humans



Throughout the history of allopathic medicine, the diagnosis of many diseases has been based upon the characteristics of cells and chemicals collected from body fluids, such as venous blood (left), urine (top right: specimen jar), or cerebrospinal fluid (bottom right - spinal tap).

The term “biomarker” refers to any chemical or cell component which can be measured before death, in order to provide an accurate signal that a disease is present.

What physicians desperately need at this time is an objective test to confirm the presence of dementia-causing conditions (such as Alzheimer’s, Parkinson’s, or Lewy body disease) prior to death, but without the need for surgical brain biopsy.

Old and new antipsychotics *all* increase Alzheimer's proteins…

Protein changes in antipsychotic recipients, relative to drug-free controls:

	source	biomarker	change
Austria 2005	(CSF)	tTG	↑ 200-400%
Italy 2005	(CSF)	tau	↑ 24%
USA 2002	(blood)	apoD	↑ 58%

CSF = cerebrospinal fluid

Researchers around the world have been working to establish an accurate but non-invasive test for the diagnosis of Alzheimer's disease. Several biomarkers have been suggested for this purpose, including spinal fluid levels of specific proteins (tissue transglutaminase and tau) and blood levels of apoD.

In several studies that have investigated antipsychotic drug effects, old and new medications have been found to provoke increased levels of biomarkers which are associated with Alzheimer's disease.

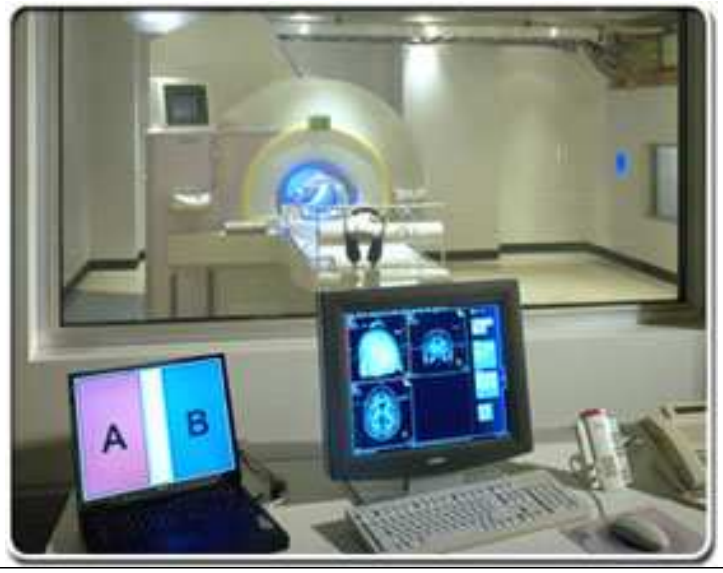
tTG = tissue tranglutaminase

an enzyme which cross-links proteins, including components of tangles and plaques. Some scientists have speculated that tTG is a cause of, or marker for, programmed cell death.

tau = component of intracellular (neuronal) neurofibrillary tangles

apoD = component of compact beta-amyloid plaques

Neuroimaging
(brain scans)



Neuroimaging techniques provide another tool for diagnosing dementia-related diseases in living subjects.

Various forms of equipment have been developed, all of which rely upon the properties of chemistry and physics to reproduce two-dimensional images of brain structures. Within the field of neuropsychiatry, radioactive (CT, PET, and SPECT) and non-radioactive (MRI, MRA) methods are commonly employed in order to track changes in the appearance of the brain.

This picture shows an MRI machine (Magnetic Resonance Imaging).

Using MRI technology, scientists are able to discern the features of different components within the brain (e.g., white matter vs. gray matter, fluid vs. solid tissue). The goal of anatomical studies is to take "snapshots" of the brain in order to identify normal or abnormal structures. So-called "functional" brain scans (fMRI) compare changes in blood flow which accompany specific activities or states of mentation.

Numerous studies…

Without exception, “before and after” brain scans have revealed shrinkage (atrophy) of the brain under the influence of *old or new* antipsychotic drugs

In some cases, patients have experienced a 4-9% reduction in volume in < 3 years

Over the past 20 years, numerous brain scan studies (CT and MRI) have evaluated the anatomy of patients following new exposures to antipsychotic drugs.

Without exception, study designs that have compared anatomical changes “before” and “after” the use of these pharmaceuticals have revealed shrinkage of the brain under the influence of conventional (old) and/or newer (so-called “atypical”) drugs.

In some studies, patients have experienced a 4-9% reduction in brain volume in less than three years.

[That the drugs are the cause of these changes, rather than an underlying disease process, is strongly implied by the research involving animals. Recall the University of Pittsburgh investigation, where monkeys exposed to Haldol or Zyprexa for 1 ½ to 2 years experienced a 10% reduction in brain volume and brain weight.]

Given the fact that antipsychotic drugs are no longer used only for psychosis (indeed, academic psychiatrists have been touting the drugs for control of aggression, irritability, and insomnia), and given the fact that their use in American children has increased *five-fold over the past two decades, one might reasonably expect that the toxicities of these drugs would become a central focus of concern and debate.

As far as this writer has been able to discern, however, neither the U.S. medical establishment, nor the various leaders of government, have seriously questioned the legitimacy of a national health policy which accepts and extends the use of antipsychotic drugs in preschoolers, children, and teens.

*from 0.2% of non-institutionalized youths in 1996-1997 to approximately 1% of non-institutionalized youths in 2004-2005

NIMH / UCLA study
child onset schizophrenia

- Using sophisticated neuroimaging methods (3D “cortical mapping”), longitudinal studies were performed on three groups of adolescents

- Goal: check changes in brain anatomy
  over time (baseline, 2.3 years, 4.6 years)

The previous point is well illustrated by the work of researchers affiliated with the National Institute of Mental Health and UCLA (University of California, Los Angeles).

Using a sophisticated neuroimaging technique known as 3-dimensional cortical mapping, the investigators performed a series of MRI brain scans in an effort to track changes in anatomy over time.

Children received brain scans at entry into the study (baseline), and again at repeated intervals of approximately 2 and 5 years.

Multiple brain scans > age 13.5 to 18

Study Design:
12 children with Childhood Onset Schizophrenia
(onset of symptoms before age 12)
all had histories of poor response to / intolerance
of at least two typical antipsychotic

10 children with transient psychosis
mood and behavioral problems

12 age & gender matched "normal" controls

Psychiatric patients received treatment with the following antipsychotic drugs: risperidone, olanzapine, or clozapine.

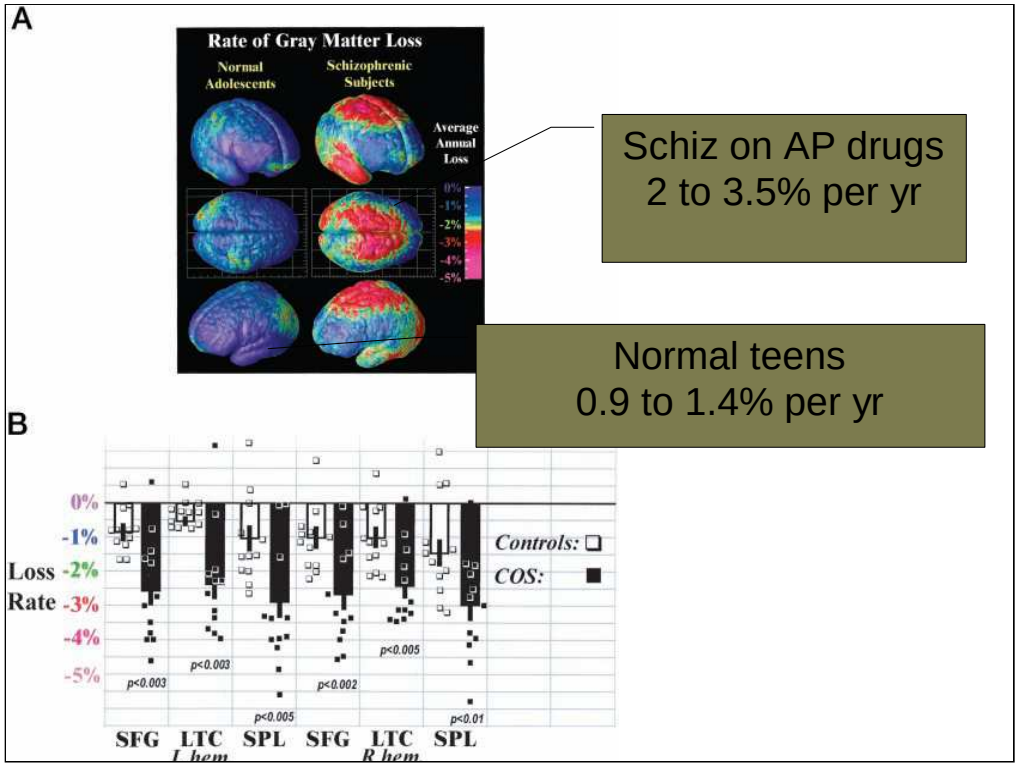
The study compared the neurodevelopment of three groups of children as they matured from the ages of 13.5 to 18 years.

In this specific protocol, individual brain scan changes were "pooled" to create a database for each group. Computer software was used to create colorful graphics which reflected shrinkage (atrophy) of the cortical surface of the brain. [Recall the Tootsie Roll lollipop candy coating = cortical surface].

Group One: 12 children with Childhood Onset Schizophrenia --
all of these children had histories of negative responses to at least two conventional (first generation) antipsychotics

Group Two: 12 age-matched, gender-matched non-psychiatric controls

Group Three: 10 children with Psychosis Not Otherwise Specified --
these children displayed mood and/or behavioral problems but never met the *DSM* criteria for schizophrenia; these children had also failed at least 2 trials of first-generation drugs



When compared to the normal controls, the teenagers exposed to antipsychotic drugs experienced accelerated reductions in cortical surface area (2 to 3.5% per year). The red zones (above, right) demonstrate the brain regions where gray matter loss was advanced.

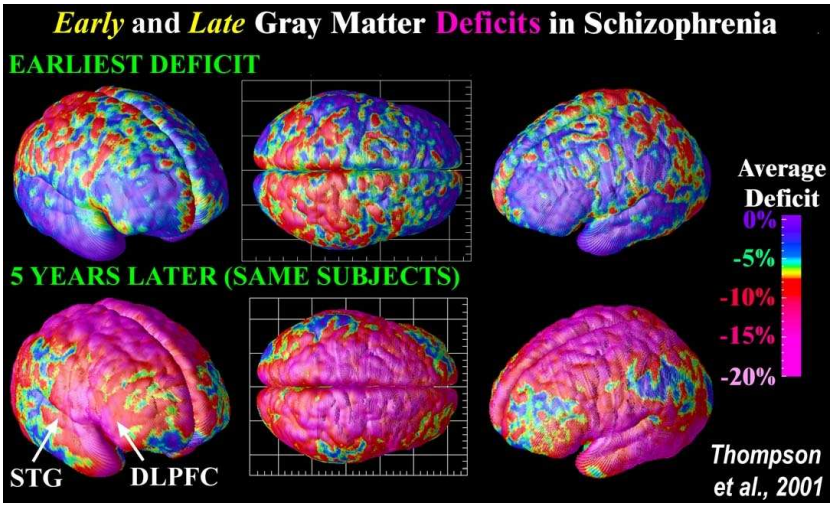
Although normal teenagers also experienced some reduction in surface area (green), their rate of change was 2-3x less than the medicated children with schizophrenia, and was consistent with *expected (normal) development.

	cortical gray matter loss per year
Schizophrenia	2 to 3.5% per year
Normal Controls	0.9 to 1.4% per year

•normal development = as neurons become myelinated during and beyond puberty, the ratios of white to gray matter increase; at the cortical surface, this results in the apparent “thinning” of gray matter

Gray Matter Loss Due to "Disease"

Thompson et al (2001) – multiple scans of teens (aged 13.9 to 18.6)
UCLA & NIMH



This slide depicts the progression of gray matter deficits (cortex) of the schizophrenia group over a period of five years. Red and pink zones (frontal, parietal, and temporal lobes) show the greatest areas of shrinkage, relative to normal controls.

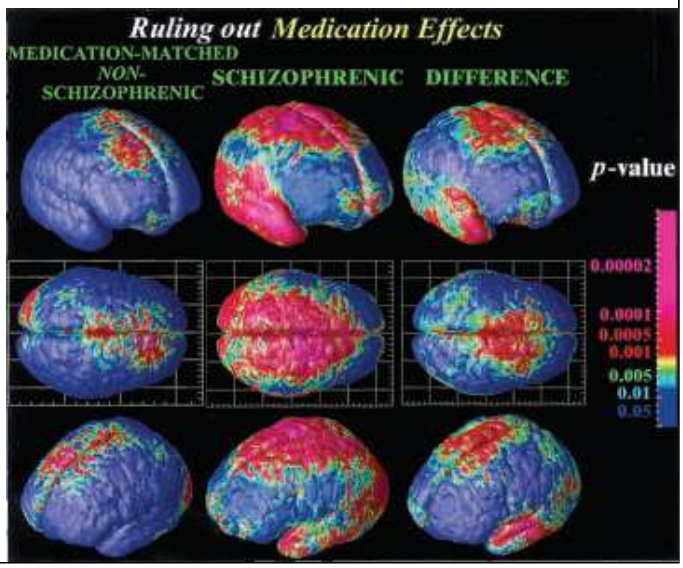
Although the researchers were quick to attribute these findings to the patients' "underlying" condition (schizophrenia), it is important to appreciate the study design. All of these teenagers had failed at least two previous trials of antipsychotics prior to the first brain scan. In their publication, Thompson et al did not divulge details about the age-of-onset, duration, or doses of past pharmaceuticals. Nevertheless, the fact that these exposures had occurred prior to age 14 makes it difficult to accept the researchers' conclusion that the observed abnormalities were not the result of prepubertal exposures to neurotoxins.

Reduced Exposure to APs
no gray matter deficit in temporal lobe

(Med Matched ?)

Psychosis NOS
n=10
2 were drug-free
at baseline and f/u
7.5% ↓

Schizophrenia
n=12
4.6 yrs + of NLs
13.0% ↓



In an attempt to discern which "brain abnormalities" might be attributable to schizophrenia (mental condition) rather than drug-treatment, the researchers compared changes in the Schizophrenia Group relative to a group of children with transient psychosis (Psychosis Not Otherwise Specified).

It is significant that the published paper by Thompson et al (PNAS, 2001) reveals that 20% (2 of 10) of the Psychiatric Control Group remained drug-free throughout the study. However, the authors did not confirm that an equal number of patients in the Schizophrenia Group avoided antipsychotic drugs.

Thus, when the researchers discovered less severe deficits in the Psychiatric Controls after five years (7.5% reduction in frontal gray matter relative to normal children, versus 13% reduction for the Schizophrenia Group), it is far from clear that these between-group differences were due to different "underlying" mental illnesses.

Notwithstanding this problematic issue, however, the disturbing fact remains that both groups of psychiatrically medicated children experienced the progressive loss of cortical gray matter in the context of continuing antipsychotic drug use.

Recap of Lecture

I. Major Classes of Psychiatric Drugs
II. America's Drug Problem
III. Killing the Mentally Ill
IV. Psychiatric Drug Toxicity

This presentation has focused on four major themes.

I. Excluding chemicals which are used to treat addiction (e.g., Antabuse, methadone), there are five major classes of psychiatric drugs: antidepressants, antipsychotics, anti-anxiety (sedative/hypnotics), mood stabilizers, and stimulants.

II. Americans account for 5% of the world's population yet they consume the majority of the world's prescription drugs. Even when taken precisely as recommended and prescribed, pharmaceuticals are the third leading cause of death in the U.S.A. each year.

III. Compared to mentally healthy individuals of the same age, patients who receive treatment within America's public mental health system die 13 to 30 years earlier than expected; die in higher numbers each year; and experience higher rates and combinations of disabling medical conditions.

IV. Psychiatric drugs elevate the risks of early death and serious medical disease. Evidence from animal experiments, human autopsies, brain scans, and biomarkers converge on the finding that antipsychotic drugs – America's top-selling drugs in 2009 – damage the brain by killing neurons. Recent evidence also suggests that antipsychotic drugs promote the defining features of Alzheimer's disease.